MULTI-Omics Analysis Reveals COX5A as a Biomarker of Disease Activity and Organ Damage of Lupus

Keywords: Systemic lupus erythematosus, Biomarkers

Background: Systemic Lupus Erythematosus (SLE) is a heterogeneous systemic autoimmune disease with protean clinical manifestations[1]. Although the long-term outlook of SLE patients with SLE has been greatly improved, increased organ damage is associated with poor prognosis in a number of patients. The type I interferon signature, a hallmark of SLE, is not an ideal treatment target or outcome predictor[2, 3], suggesting other critical immunological pathways might contribute to disease pathogenesis.

Objectives: To explore key immunological pathways and gene markers in SLE more precisely, we performed a systematic analysis of transcriptional data from 27 immune cells in the blood and from single cells in the skin and kidney.

Methods: We included a large RNA-seq data from a total of 64 SLE and 62 control with 27 immune cells. Integrated analyses were conducted to find key pathways and drivers genes in SLE pathogenesis. The expression of COX5A between SLE phenotypes was compared in two independent cohorts. Single-cell RNA sequencing (scRNA-seq) data from skin and kidney were used to further determine the association of COX5A expression with organ damage.

Results: We found that lymphocytes in SLE showed an overall active immune-no-metabolic state when compared to healthy controls, and oxidative phosphorylation (OXPHOS) is the most significant metabolic pathway that differs between SLE and HC, especially for effector T cells. Besides, the OXPHOS enrichment score was significantly correlated with IFN response molecular signature across various T cell subtypes. Particularly, we identified an OXPHOS hub gene, COX5A, as a key driver in SLE T cells. COX5A expression was significantly higher in effector T cells than those in naïve T cells and showed associations with SLE clinical phenotypes including disease activity index, flare, and organ damage. Furthermore, we revealed that high expression of COX5A in T cells contributes to skin and kidney involvement of SLE through scRNA-seq analysis.

Conclusion: Our results identified OXPHOS signature is a prominent feature in SLE T cells. The key gene of OXPHOS, COX5A, showed associations with IFN response molecular signature, severity, skin, and kidney involvement of SLE, which supported COX5A as a potential candidate biomarker of severity and organ damage of SLE.

REFERENCES:

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ENTEROCOCCUS GALLINARUM IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

Keywords: Descriptive studies, Outcome measures, Systemic lupus erythematosus

Background: Systemic Lupus Erythematosus (SLE) is associated with epithelial defects and disrupted intestinal barrier, risking bacterial translocation and promoting systemic inflammation, known as dysbiosis, which is associated with increased disease activity [1]. Enterococcus gallinarum has been previously linked to gastrointestinal autoimmune diseases like chronic hepatitis and primary sclerosing cholangitis [2]. However, little is known about E. gallinarum prevalence in SLE.

Objectives: To describe the prevalence of E. gallinarum in SLE stool samples, as well as clinical and laboratory characteristics.

Methods: A cross-sectional, descriptive study was conducted at the University Hospital “Dr. José Eleuterio González”, in northern Mexico. We included adult patients who met current criteria for SLE and had recent (<3 months) paracilinical routine tests, including acute phase reactants. Patients with other autoimmune other chromatin components, like histones and nucleosomes. These antibodies are known to characterize a SLE subgroup with early disease onset and increased occurrence of nephritis.

Objectives: We investigated how anti-nuclear autoantibody (ANA) specificities associate with pro-inflammatory cytokines in two ethnically different cohorts of SLE patients, from Sudan and Sweden.

Methods: We included 93 Sudanese and 480 Swedish SLE patients. Serum levels of autoantibodies against dsDNA, Sm, the 5Sm/1RNP complex, 1RNP, SSA/Ro52, SSA/Ro60, SSB/La, ribosomal P, PCNA and histones were quantified with a bead-based multiplex immunoaassay; with positive reactions determined as above the 98th percentile among respective national controls. In the Swedish cohort another beaded-multiplex immunoaassay including anti-nucleosome antibodies was also used. Relative levels of 73 plasma biomarkers were determined with Proximity Extension Assay technique except for Interferon gamma-induced protein (IP-10) in the Swedish cohort that was quantified by ELISA. Adjusted p values were considered significant when <0.05.

Results: Among Sudanese patients, levels of 5/73 biomarkers showed significant associations to ANA-associated antibodies. Anti-histone antibodies showed the strongest positive correlations with interferon-inducible factors (monocyte chemoattractant protein [MCP-1] and IP-10), monocyte chemoattractant protein-3 (MCP-3) and S100 calcium-binding protein A12 (S100A12), and negative correlation with stem cell factor (SCF); FF(p values) were 0.15(0.04), 0.18(0.008), 25(0.0001), 0.13(0.04) and 0.31(<0.0001) respectively. Biomarker associations remained significant for anti-histone antibody after adjustment for age and sex. Also, anti-dsDNA antibodies associated with MCP-3 (0.13(0.04)), IP-10 (0.13(0.03)) and S100A12 (0.13(0.04)), but when combining with anti-histone in the same regression model, anti-dsDNA associations were lost while anti-histone antibodies remained. Positive associations with lower FF values were found also for anti-ribosomal P antibodies with MCP-1, MCP-2 and C-C motif ligand 19 (CCL-19), and for anti-Sm with IP-10. Validation analysis among Swedish patients for MCP-1, IP-10, S100A12 also demonstrated significantly stronger associations to anti-histone and anti-nucleosome antibodies compared to anti-dsDNA and other ANA specificities, and in combined regression models, anti-dsDNA either became non-significant or considerably less significant than anti-histone/nucleosome antibodies. When excluding anti-histone or anti-nucleosome positive patients, the associations between interferon-inducible factors MCP-1/IP-10 and anti-dsDNA were lost. In contrary, when excluding anti-dsDNA positive patients, associations with anti-histone and anti-nucleosome remained significant. S100A12 associations with anti-dsDNA antibodies remained significant after exclusion of anti-histone positive patients, but were lost when excluding anti-nucleosome positive patients.

Conclusion: Using uni- and multi-variate analyses as well as patient stratification, levels of mainly IFN-induced inflammatory biomarkers correlate stronger with anti-histone and anti-nucleosome antibodies compared to other ANA specificities including anti-dsDNA. Our results, from two lupus cohorts with different ethnicities, suggest that autoantibodies against DNA-complexes or DNA-associated proteins rather than anti-dsDNA antibodies per se may drive the induction of the interferon signature in SLE.

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